REMARKS/ARGUMENTS

Claims 1-12 are pending in the application: of which, claims 5-12 were withdrawn from consideration; and claims 1-4 were examined, and now stand rejected. Claim 1 has been amended herein. Support for the amendment can be found for example at paragraphs 5, 26, and 248 of the specification.

Specification

Applicants have amended the specification to address the point raised by the Examiner.

Claim Rejections - 35 USC §101, Utility

Claims 1-4 are rejected under 35 USC §101, allegedly because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Applicants respectfully disagree, for at least the following reasons.

A) THE PRESENT CLAIMS HAVE UTILITY FOR IDENTIFYING COMPOUNDS WITH PHARMACOLOGICAL ACTIVITY

According to the Office Action, the utility of the claimed invention is to determine the binding between alpha adrenergic receptors (AARs) and PDZ proteins, such that binding can be modulated for therapeutic purposes. However, the Office Action asserts such a therapeutic utility is not substantial for two reasons: (1) the invention amounts to no more than a starting point for further research, and (2) there is no reasonable correlation between binding and modulation of AAR activity by altering such binding. Applicants disagree. Each of these points is discussed below.

i) The claimed invention is more than a starting point for further research

The first alleged reason is that the invention amounts to no more than a starting point for further research. Applicants disagree. Applicants note that the Office Action acknowledges that the claimed methods of *in vitro* testing can be used to identify modulators of binding between A2ARs and PDZs. This in itself provides utility to the claims. As the Federal Circuit, in *Cross v. Iizuka*, 753 F.2d 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985), commented on the significance of data from *in vitro* testing:

> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility . . . Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.

ii) The claimed methods can successfully identify physiologically relevant interactions

Second, the Office Action also asserts that such a utility is not substantial because there is no reasonable correlation between binding and modulation of AAR activity by altering such binding, especially since the art questions the physiological significance *in vivo* of a binding interaction identified *in vitro*. In support of this assertion, the Office Action discusses the results of Schepens *et al.* and Pupo *et al.*. Schepens *et al.* apparently observed binding *in vitro* between a 114 amino acid C-terminal fragment of AAR-1A and nNOS; but the relevance of this apparent interaction was later questioned by Pupo *et al.* who found that binding of nNOS to AAR-1A occurred even in the absence of the C-terminal portion, and that nNOS did not appear to be involved in the effect of transfected AAR-1A on mitogenic signaling in cells.

Contrary to the Office Action's conclusion, however, the *in vitro* binding results of the claimed methods are indeed reasonably predictive of physiologically relevant interactions *in vivo*. Although the Office Action focuses attention on one single binding interaction identified

in vitro between an AAR and a PDZ protein, for which the *in vivo* relevance was later questioned, this is insufficient to demonstrate a lack of utility. As the MPEP makes clear, "[i]f an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate." MPEP 2107.01, citing to *In re Brana*, 51 F.3d 1560. There are clear indications that the claimed *in vitro* methods will succeed in identifying binding interactions that are physiologically relevant *in vivo*. For example, Applicants have used analogous methods to identify physiologically relevant interactions between other PL ligands such as HPV E6 and cellular PDZs. (*See* related PCT application No. US02/24655, to which the present application claims priority). In addition, Applicants also used such methods to identify inhibitors of E6-PDZ binding, which showed a therapeutic effect *ex vivo* (specifically, the inhibitor were seen to block the oncogenic transformation of cells by E6). *See* US 2004/0229298, which also claims priority to PCT/ US02/24655, at Example 10. Accordingly, such methods have been successfully applied to other PL ligands and have not only resulted in the identification of physiologically relevant interactions with PDZ proteins, but have also led to the identification of therapeutic modulators of such interactions.

Similarly, one embodiment of the claimed methods involves a yeast two-hybrid assay. The yeast two-hybrid assay has been accepted by those of skill in the art as reasonably correlating with physiologically relevant *in vivo* binding (*See, e.g.*, Sprinzak, et al. (2003), J. Mol. Biol., 327, 919–923, concluding that approximately 50% of the interactions identified by the yeast two-hybrid system are biologically relevant).

Finally, A2AR antagonists have a well-established therapeutic use. *See, e.g.*, Erb *et al.*, Neuropsychopharmacology (2000) 23:138-150. The Office Action appears to have implicitly acknowledged as much by lack of assertions to the contrary.

Just as such methods have done for other PL ligands in the past, the claimed methods have utility in providing a system to identify antagonists of a physiologically relevant interaction of A2AR. Even if such antagonists require further testing *in vivo*, the claimed methods are of immediate benefit in providing in providing a selection of pharmacological active compounds for further testing.

B) THE PRESENT CLAIMS ALSO HAVE OTHER UTILITIES

Taking for example the first five PDZ proteins that are listed as binding to alpha 2 adrenergic receptor in Table 8A (*i.e.*, AF6, AIPC (also called PIN1), APXL1, CARD14 and CNK1), commercial antibodies are publicly available to all five PDZ proteins.[1] The existence of commercial antibodies shows a real-world, established utility for a method of detecting of all five target proteins. The claimed methods thus have utility as research tools, since they can be used to detect or quantify a PDZ protein in a sample that is bound by the AAR peptide. As the present application explains, the claimed detection methods can be applied in a variety of assay formats such as ELISA immunoassays, immunoprecipitation, Biacore, Fluorescence Polarization (FP), Fluorescence Resonance Energy Transfer (FRET) and Western blot assays.

One example of a practical application for detection of such PDZ proteins is tissue typing. Many of the PDZ proteins listed in Table 8A as being bound by the AAR peptide are tissue-specific markers. For instance, NeDLG is a neuronal and endocrine tissue-specific protein. *See, e.g.*, Oncogene 14 (20), 2425-2433 (1997).

In addition, other PDZ proteins that are bound by AAR peptide are disease markers. For instance, AIPC is a protein that is highly expressed in prostate cancer. *See, e.g.*, Cancer Res. 61 (6), 2390-2394 (2001).

Accordingly, the claimed detection methods can be used for instance to tissue-type a sample or diagnose a disease state. For the above reasons, therefore, Applicants request that the rejection for lack of utility be withdrawn.

Claim Rejections - 35 USC §112, Enablement

Claims 1-4 also stand rejected for lack of enablement. The claims specify detection of binding between a PDZ protein and a "C-terminal PL sequence" of an alpha adrenergic receptor ("AAR"). According to the Office Action, the metes and bounds of a "C-

[1] See, e.g., http://www.biocompare.com/jump/ 2045/Antibodies.html (type in antigen of choice). *See also* http://www.biocompare.com/matrixsc/3194/2/6/47816/AF-6.html; http://www.biocompare.com/matrixsc/3194/2/6/28464/Pin1.html; http://www.biocompare.com/matrix.asp?scid=2&catid=3194; http://www.biocompare.com/matrix.asp?catid=3194&scid=2&search=card14&ss=0&type=0&type=0&type=0&type=0; http://www.biocompare.com/matrix.asp?catid=3194&scid=2&search=CNK1&ss=0&type=0&type=0&type=0&type=0

terminal PL sequence" are not defined in the specification, nor does the specification define this term to exclude internal sequences within the (allegedly undefined) C-terminus of an AAR. The Office Action has therefore construed the claims to cover *any* PL sequence from an AAR and variants thereof (allegedly a large genus), and asserts that the specification does not teach any sequences, other than SEQ ID NOs: 26, 27 and 28, that can bind PDZ proteins.

It is believed that the underlying issue is the manner in which the Examiner is interpreting the claims. Applicants have clarified claim 1 to recite a polypeptide "containing an alpha 2 adrenergic receptor C-terminal peptide sequence comprising the last 3 consecutive amino acids at the C-terminal end of SEQ ID NO: 26, SEQ ID NO: 27 or SEQ ID NO: 28" in order to more clearly specify that the polypeptide is in fact derived from the very C-terminal end of AARs.

Applicants submit that the claims as amended herein do not encompass such a large number of variants as the Office Action contends and request that this rejection be withdrawn.

Claim Rejections - 35 USC §112, written description

Claims 1-4 are also rejected for lack of written description. The Office Action acknowledges that Applicants had possession of a polypeptide comprising SEQ ID NOs: 26, 27 and 28, but contends that the claims extend beyond this disclosure.

In response, Applicants have amended the claims to recite a polypeptide containing an alpha 2 adrenergic receptor C-terminal peptide sequence comprising the last 3 consecutive amino acids at the C-terminal end of SEQ ID NO:26, SEQ ID NO:27 or SEQ ID NO:28, and submit that the specification clearly discloses such sequences. Although the Office Action asserts that the present application "does not teach any smaller fragments of SEQ ID NOs: 26, 27 and 28," Applicants respectfully disagree. Although only the binding of SEQ ID NOs: 26, 27 and 28 to PDZs was actually tested, the specification clearly indicates that smaller fragments were contemplated and within Applicants' possession, including fragments as small as 2, 3, 4, or 5 amino acids in length. *See, e.g.*, paragraph 26 of the specification. In addition, Applicants had already demonstrated that a diverse variety of C-terminal PL sequences of only 3 amino acids can bind to corresponding PDZ proteins. *See, e.g.*, US 2005/0282743 at Example 6;

20060148711 at Example 5; and U.S. App. No. 10/553,028. The Examiner thus lacks reasonable grounds for a conclusion that shorter fragments are not described.

Applicants thus request that this rejection be withdrawn.

Claim Rejections - 35 USC §102, Anticipation

Claims 1-4 are also rejected under Section 102 as anticipated by Schepens *et al.*, 1997, FEBS Letters, 409:53-56.

In response, Applicants have amended claims 1-4 to recite a method of detecting interaction between alpha-**2** adrenergic receptors and PDZ proteins

By contrast, Schepens *et al.* only observed a lone interaction of an alpha-**1A** adrenergic receptor (AAR-1A) with the PDZ protein nNOS. Strikingly, Schepens failed to observe an apparent binding of nNOS with any other AARs. Schepens *et al.* did not even observe an apparent binding of nNOS to other alpha-1 adrenergic receptors 1B and 1C, let alone binding to alpha-**2** adrenergic receptors. The results of Schepens *et al.* led Pupo *et al.* to believe that binding of AAR-1A to nNOS was probably subtype-specific, and limited to AAR-1A alone. *See* Pupo *et al.* (discussed in the Office Action), at page 2, first paragraph.

In addition, as the specification explains, the PL motifs found in alpha-**2** adrenergic receptors are different from those alpha-**1** adrenergic receptors, implying binding to different sets of PDZ proteins. *See paragraph 586 of the specification.*

Accordingly Schepens *et al.* fail to discuss or suggest Applicants' claimed methods.

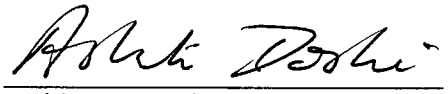
Claim Rejections - 35 USC §103, Obviousness

Claims 1-4 are also rejected under Section 103 as obvious over Schepens *et al.* in view of Suzuki *et al.* (Oncogene 18:1239-1244 (1997)). Suzuki allegedly teaches a method of detecting protein-protein binding using a "Far Western" technique involving the separation of proteins from a cell extract and probing with a labeled peptide.

As discussed, however, Schepens *et al.* do not disclose or suggest the interaction of alpha-2 receptors with PDZs. Suzuki *et al.* fails to compensate for these deficiencies.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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